

**REMARKS**

Upon entry of the amendments made herein, claims 1-4, 6-7, 9-14, 19, 21, 23-26, 30-40, 56-68, 82, 103-112, 117-143, 145-147 and 149-158 are pending in this application. Claims 1, 2, 4, 19, 21, 26, 30, 32, 34, 39, 59, 60, 62, 66, 67, 82, 103-107, 109-112, 117-140, 142, 145-147, 149-151, 153 and 154 are currently amended. New claims 155-158 have been added. Claims 113-116 have been canceled herein without prejudice or disclaimer while claims 5, 8, 15-18, 20, 22, 27-29, 41-55, 69-81, 83-102, 144 and 148 were previously canceled.

Claims 1 and 82 were amended to further define the invention. Support for the amendments can be found, *e.g.*, in Table 2 on pages 42-53 of the specification as filed.

Claim 32 was amended to further define the invention. Support for this amendment can be found, *e.g.*, on page 7, lines 11-14 and on page 6, line 23 through page 7, line 9 of the specification as filed.

Claim 39 was amended to maintain proper antecedent basis throughout the amended claim set. Support for this amendment can be found, *e.g.*, in claim 34 as originally filed.

Claims 2, 4, 19, 21, 26, 30, 34, 59, 60, 62, 66, 67, 103-107, 109-112, 117-140, 142, 145-147, 149-151, 153 and 154 were amended to correct inadvertent typographical errors and/or to correct claim dependencies.

New claims 155-158 have been added. Support for the claims can be found, *e.g.*, on page 11, lines 4, 9, 11, 12 and on page 12, lines 34-35.

Accordingly, no new matter has been added.

**Double Patenting**

Claims 1-4, 6, 7, 9-14, 19, 21, 23, 24, 30-40, 82, 140-143 and 145-154 remain provisionally rejected under obviousness-type double patenting as being unpatentable over claims 1 and 26-54 of co-pending Application No. 10/839,023.

Applicants have previously canceled claim 148. Therefore, with respect to this claim, the rejection is moot.

With respect to claims 1-4, 6, 7, 9-14, 19, 21, 23, 24, 30-40, 82, 140-143 and 145-147 and 149-154, Applicants traverse the rejection and note that this rejection is a provisional double patenting rejection for which the M.P.E.P. at § 804 section I, subsection B1 provides as follows:

If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. If the ODP rejection is the only rejection remaining in the later-filed application, while the earlier-filed application is rejectable on other grounds, a terminal disclaimer must be required in the later-filed application before the rejection can be withdrawn.

The instant application claims priority to U.S. Application No. 09/823,884 (now U.S. Patent No. 6,818,634), filed on March 30, 2001. The cited co-pending Application No. 10/839,023 claims priority to U.S. Application No. 09/895,857 (now U.S. Patent No. 6,846,939), filed on June 29, 2001. Thus, the instant application is the earlier-filed application with respect to co-pending Application No. 10/839,023. Accordingly, should the Examiner find the present claims allowable in view of the arguments included herein, Applicants respectfully request withdrawal of the provisional double patenting rejection.

### 35 U.S.C. §103

Claims 1, 7, 11, 18, 23-25, 66 and 67 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barden *et al.* (J. Med. Chem., 1994, v.37, no.20, p. 3205-3211) ("Barden") in view of Silverman, R. B. (The Org. Chem. Of Drug Design and Drug Action, Academic Press, Inc., SanDiego, 1992, p. 4-51) ("Silverman").

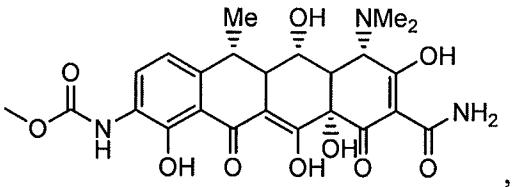
The Examiner stated that Barden teaches a compound where R<sup>9a</sup> is methyl. Furthermore, the Examiner has asserted that Barden also teaches that modification at the R<sup>9a</sup> position varied and increased potency with lengthening of the alkyl chain length. (See Office Action at p. 5). In addition, the Examiner alleged that Silverman teaches how lengthening a carbon chain increases pharmacological effects. (See Office Action at p. 5). Finally, the Examiner described the difference between the Barden compound and the current claims to be a CH<sub>2</sub>CH<sub>2</sub> group at the R<sup>9a</sup> position. (See Office Action at p. 5).

Applicants have previously canceled claim 18. Therefore, with respect to this claim, the rejection is moot. With respect to claims 1, 7, 11, 23-25, 66 and 67, Applicants traverse the rejection.

In 2008, the Federal Circuit revisited the issue of obviousness in the context of chemical compounds in *Eisai Inc. v. Dr. Reddy's Laboratories, Inc. and Teva Pharmaceuticals USA, Inc* (Fed. Cir. 2008). The Court stated

Where, as here, the patent at issue claims a chemical compound, the analysis of the third *Graham* factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art compounds. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006) (noting that, for a chemical compound, a *prima facie* case of obviousness requires “structural similarity between claimed and prior art subject matter...where the prior art gives reason or motivation to make the claimed compositions” (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc))). Obviousness based on structural similarity thus can be proved by identification of some motivation that would have lead one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). In keeping with the flexible nature of the obviousness inquiry, *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007), the requisite motivation can come from any number of sources and need not necessarily be explicit in the art. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007). Rather “it is sufficient to show that the claimed and prior art compounds possess a ‘sufficiently close relationship...to create an expectation,’ in light of the totality of the prior art, that the new compound will have ‘similar properties’ to the old.” *Id.* (quoting *Dillon*, 919 F.2d at 692).

The pending claims are drawn to 7- or 9-carbamate substituted tetracycline compounds. Specifically, independent claim 1 is drawn to substituted tetracycline where R<sup>9</sup> is hydrogen or NR<sup>9a</sup>C(=Z')ZR<sup>9a</sup>. The remaining claims subject to this rejection depend, directly or indirectly, from this claim. The Examiner cites the following compound as relevant:



from Barden (compound 12) where ZR<sup>9a</sup> is methoxy (R<sup>9a</sup> is methyl). Compound 12 is one of 15 compounds described in Table 1. The 14 remaining compounds are not cited as relevant.

Barden does not provide sufficient motivation or any objective reason to select and/or modify compound 12 to arrive at the currently claimed compounds. The data included in Table 1 of Barden would not motivate one of skill to select compound 12 because 9 out of the 10 cell lines studied for antibacterial activity show compound 12 to have inferior properties relative to at least one other compound in the table.

In addition, Barden teaches away from the invention, stating that *N,N*-dialkylglycinamides, and not the currently claimed compounds, exhibited the highest activity in the assays described therein. (*See* Barden at page 3207, left column, lines 2-4). One of ordinary skill would not select compound 12 as a candidate for further modification and/or study. Thus, it would not have been obvious to single out the particular compound (compound 12) identified by the Examiner, let alone to select this compound for use in the treatment of a tetracycline responsive state.

In addition, Barden does not provide sufficient motivation or any objective reason to modify compound 12 to arrive at the claimed invention. Barden's teaching that lengthening the alkyl chain at the R<sup>9a</sup> position results in increased potency is exemplified with reference to 3 unrelated compounds (compounds 17, 18 and 21) in Table 1. None of these compounds include a 9-carbamate tetracycline structure. Moreover, Table 1 does not include sufficient data to draw a comparative conclusion with respect to 9-carbamate tetracyclines, because only one 9-carbamate tetracycline structure is described. Thus, it would not have been obvious to single out the particular compound (compound 12) identified by the Examiner, or to choose lengthening of the R<sup>9a</sup> carbon chain as a preferred or otherwise desirable means for modifying this compound. As such, the skilled artisan would not have been motivated by the teachings of Barden to modify compound 12 to arrive at the claimed compounds, nor would the skilled artisan be motivated to use these modified compounds in the treatment of a tetracycline responsive state.

The Examiner stated that Silverman teaches how lengthening a carbon chain can increase pharmacological effects.

As described above, Barden fails to provide any motivation or objective reason to select and/or modify compound 12. Silverman does not cure the deficiencies of Barden. According to Silverman, lengthening a carbon chain can also decrease potency due to increased lipophilicity or the formation of micelles. (*See* Silverman at page 16 and Table 2.1 on page 17). Moreover, Silverman teaches a generic description of homologation of a

substituted resorcinol and a mandelic acid ester and there is no indication that the same principle holds true for 9-carbamate substituted tetracycline compounds. The currently claimed 9-carbamate substituted tetracycline compounds are chemically unrelated to the single-ring aromatic compounds described in Silverman. Therefore, Silverman provides no motivation or objective reason to select and/or modify compound 12 to arrive at the claimed invention. Thus, Applicants submit that the combination of Barden and Silverman does not render claims 1, 7, 11, 23-25, 66 and 67 obvious. Applicants request reconsideration and withdrawal of the rejection.

### **35 U.S.C. §112**

Claims 1, 32 and 82 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Applicants traverse the rejection.

Claims 1 and 82 have been amended to remove substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkylamino, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclic and substituted or unsubstituted heteroaromatic groups from the definition of R<sup>9a</sup>.

Claim 32 has been amended to correct the claim dependency and to properly describe the depicted moiety as a substituted alkyl group.

The Examiner stated that claims 1 and 82 contain amendments including deleting part of a proviso and altering the scope of R<sup>9a</sup> to C<sub>3</sub>-C<sub>10</sub> alkyl without sufficient support in the original disclosure. (See Office Action at p. 7). The Examiner also stated that claim 32 contains an amendment which creates an unsupported new subgenus.

### **Claims 1 and 82 Proviso**

Applicants previously amended the proviso in claims 1 and 82 to read “provided that R<sup>9</sup> is not hydrogen when R<sup>7</sup> is hydrogen.” (See Response to non-final Office Action filed on August 8, 2008). Prior to the amendment, the proviso read “provided that at least one of R<sup>9</sup> is not hydrogen when R<sup>7</sup> is hydrogen.” The specification as filed reads, *e.g.*, on page 5, lines 26-27, “provided that R<sup>9</sup> is not hydrogen when R<sup>7</sup> is dialkylamino or hydrogen.” The phrase “at least one of” was previously deleted from claims 1 and 82 to clarify the proviso because it

only relates to one variable, namely R<sup>9</sup>. In addition, currently pending claims 1 and 82 are consistent with the specification as filed since neither the claims nor the above-cited passage in the specification include the phrase “at least one of.” As a result, the provisos of claims 1 and 82 are fully described in the specification.

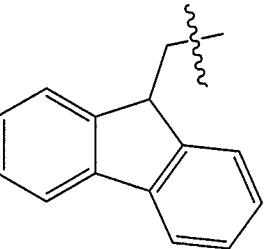
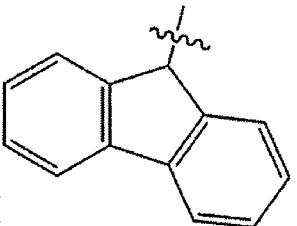
Claims 1 and 82 Scope of R<sup>9a</sup>

The current scope of R<sup>9a</sup> is supported by the original disclosure. Applicants previously amended claims 1 and 82 to include “unsubstituted C<sub>3</sub>-C<sub>10</sub> alkyl” in the definition of R<sup>9a</sup>. (See Response to non-final Office Action filed on June 21, 2007). Support for this amendment can be found, *e.g.*, on page 22, lines 19-22 of the specification as filed.

Claims 1 and 82 have been amended so that R<sup>9a</sup> is defined as: unsubstituted C<sub>3</sub>-C<sub>10</sub> alkyl, substituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted aryl. The full scope of R<sup>9a</sup> is supported by the specification and claims as originally filed. For example, compounds C, F, M, W, AA, AP, AS, BQ, BR, BS and BV of Table 2 comprise an unsubstituted C<sub>3</sub>-C<sub>10</sub> alkyl R<sup>9a</sup> group, compounds A, Y and AN of Table 2 comprise a substituted alkyl R<sup>9a</sup> group, compounds Z, AM, AQ, BJ and BT of Table 2 comprise an alkenyl R<sup>9a</sup> group, compounds X and AH of Table 2 comprise an arylsulfonyl R<sup>9a</sup> group, compound AT of Table 2 comprises an alkoxycarbonyl R<sup>9a</sup> group, compounds BE and BF of Table 2 comprise an alkoxy R<sup>9a</sup> group, compound BG of Table 2 comprises an arylcarbonyl R<sup>9a</sup> group and compounds B, D, E, I, K, L, AB, AC, AD, AE, AF, AG, AI, AJ, BB, BC, BD, BE, BF, BH, BI, BK, BL, BM, BN, BO, BP and BU of Table 2 comprise an aryl R<sup>9a</sup> group. Additional groups, such as alkynyl, are also described throughout the specification and claims as originally filed. (See *e.g.*, page 14, line 2 through page 17, line 20). Moreover, synthetic scheme 1 describes a synthetic pathway to make the claimed compounds. Thus, Applicants submit that the specification describes the currently amended claims in sufficient detail such that a skilled artisan would conclude that Applicants had possession of the claimed invention at the time the application was filed. Applicants request reconsideration and withdrawal of the rejection.

Claim 32

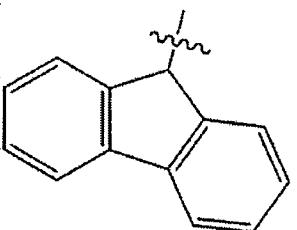
Applicants previously amended claim 32 to remove the moiety



and replace it with the moiety

Furthermore, Applicants have herein amended claim 32 to correct the claim dependency and specify that the moiety is a substituted alkyl group. Support for this claim can be found, *e.g.*, on page 6, line 23 through page 7, line 9, where the specification states  $R^{9a}$  can be substituted alkyl (such as substituted methyl) and lists aryl (such as fluorene) as a possible substituent.

Furthermore, support for this amendment can also be found, *e.g.*, on page 7, lines 11-14, where the specification reads “In a further embodiment,  $R^{9a}$  includes at least one aryl group, *e.g.*, heteroaryl, phenyl, naphthyl, fluorene, *etc.* Fluorene is a moiety of the formula:



.” (emphasis added) The language “includes” is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. (See MPEP §2111.03). Thus, the statement (that  $R^{9a}$  includes an aryl group) encompasses a substituted alkyl group at  $R^{9a}$  where the alkyl moiety is substituted with an aryl group, such as fluorene. As such, Applicants submit that the specification describes the claimed invention in sufficient detail such that a skilled artisan would conclude that Applicants had possession of the claimed invention at the time the application was filed. Applicants request reconsideration and withdrawal of the rejection.

**Note**

Applicants note that claims 26, 56, 58-65, 68 and 103-139 are currently not subject to any rejection. As such, Applicants believe that these claims are in condition for allowance.

**CONCLUSION**

Applicants respectfully submit that this application is in condition for allowance. If there are any questions regarding this amendment and/or these remarks, the Examiner is respectfully requested to telephone the Applicants' attorney/agent undersigned.

Respectfully submitted,

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